Patient preferences in treatment of recurrent singleton preterm birth

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> This monograph was funded by AMAG Pharmaceuticals, Inc. All materials have undergone peer review according to Women's Healthcare standards.

### ABSTRACT

**Purpose:** To quantify patient preferences for administration-related attributes of treatments used to reduce the risk of recurrent singleton preterm birth (PTB), and to identify drivers of treatment adherence propensity.

#### Study design and methods: A

cross-sectional study was conducted among women 18 to 44 years of age. Respondents had to qualify into one of three groups: 1) had a spontaneous PTB in the past 3 years and were not treated for it, 2) at risk of recurrent singleton PTB in the past 3 years and were treated, and 3) pregnant at the time of this study, were at risk, and were being treated. A quantitative technique for eliciting patient preferences, called discrete choice experiment (DCE), was performed using administration-related treatment attributes. Respondents were presented with hypothetical treatment options and then asked to select an

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A landmark study demonstrated a 33% reduction in delivery before 37 weeks of gestation in women with a history of singleton PTB who received weekly intramuscular injections of 17-alpha-hydroxyprogesterone caproate (17-OHPC) compared to placebo.<sup>3</sup>

overall preferred product and a product to which they were most likely to adhere.

**Results:** Overall, patients preferred treatments with faster administration times (estimate = 1.29 [95% highest posterior density interval = 0.78-1.79]), shorter needle (1.08 [0.65-1.51]), nonvisible needle (0.96 [0.40-1.54]), and subcutaneous route of administration (0.38 [0.02-0.81]). Lack of needle visibility (1.00 [0.51-1.54]), faster time for administration (0.65 [0.23-1.15]), and thinner (0.60 [0.25-0.97]) and shorter injection needle (0.56 [0.17-0.94]) were observed to drive medication adherence propensity. There were no statistically significant differences between respondent groups.

**Clinical implications:** Nursing professionals play a critical role in patient education, outcome improvement, and management regarding recurrent singleton PTB. Understanding and incorporating patients' treatment preferences into practice decisions will help empower patients and support a more patient-centric care paradigm.

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The American Congress of Obstetricians and Gynecologists (ACOG) defines preterm birth (PTB) as the birth of a live infant between 20 and 37 weeks of gestation.<sup>1</sup> In 2015, approximately one out of every ten infants was born preterm in the United States.<sup>2</sup>

A landmark study demonstrated a 33% reduction in delivery before 37 weeks of gestation in women with a history of singleton PTB who received weekly intramuscular injections of 17-alpha-hydroxyprogesterone caproate (17-OHPC) compared to placebo.<sup>3</sup> A subcutaneous autoinjector formulation of 17-OHPC, with comparable bioavailability to the intramuscular injection, was recently approved by the U.S. Food and Drug Administration (FDA).<sup>4,5</sup>

To ensure treatment adherence, nurses and other healthcare professionals must consider patient preferences,<sup>6</sup> especially when they differ from those of the providers.<sup>7</sup> Studies have reported that due to a lack of consensus guidelines for best practices in preventing PTBs, the decision to initiate adequate, timely, and appropriate care lies in the hands of at-risk women and their healthcare providers.<sup>9</sup> Evidence suggests that women suffering from high-risk pregnancies feel more satisfied with their pregnancy outcomes when they play an active role in their medical decisions.<sup>10</sup> Another study reported that the ability of nurses to support these women in decision-making was the most important contributing factor to helping them feel as though they were in control of their prenatal care.<sup>10</sup>

In addition to understanding overall patient preferences, it is equally important to appreciate how various routes of administration can affect the likelihood of adherence to treatments. A recent study reported that at least 10.9% of women at risk for PTB were unlikely to adhere to their healthcare provider's treatment recommendations.<sup>9</sup> Research indicates that nonadherence to parenteral treatments may be driven by a fear of needles.<sup>11</sup> A review article focusing on diabetic patients concluded that a fear of injections is one of the top contributors of nonadherence to injectable treatments, and that prescribing autoinjectors may mitigate this.<sup>11</sup> Similarly, a recent study among patients with type 2 diabetes reported a fear of needles, associated pain, and needle size as the most common reasons patients discontinue an injectable medication.<sup>12</sup>

Given the fear of injection needles in other disease areas,<sup>11,12,13</sup> and a recently approved subcutaneous autoinjector formulation, it is important to understand patients' preferences for treatment attributes used to reduce the risk of recurrent singleton PTB. Based on the comparative bioavailability of currently available treatments,<sup>5</sup> this study was designed to elicit patient preferences for administration-related treatment attributes using a discrete choice experiment (DCE). The study also aimed to identify administration-related factors that may impact perceived patient adherence.

## Methods Study design

A cross-sectional quantitative study approved by the Institutional Review Board at the University of Mississippi was conducted among women using a confidential online survey. Respondents created password-protected logins to track their surveys and honoraria (reward points). Any identifiable information was stored on an encrypted server and never shared with researchers or sponsors. Patient demographics collected included age, marital status, and number of PTBs.

The DCE was designed using guidelines published by the International Society for Pharmacoeconomics and Outcomes Research.<sup>14,15</sup> The DCE treatment attributes were informed by properties of currently available treatments and in consultation with clinical experts, which resulted in a six-attribute DCE design with two levels within each attribute (*Figure 1*).

This design was used to simulate hypothetical treatments by implementing choice model design macros developed by Kuhfeld using SAS 9.4.<sup>16</sup> These macros enable optimization of design efficiency, correlations between attribute levels, and the number of choice tasks.<sup>17</sup> Each survey respondent was asked to sequentially complete all 6 choice tasks, presented in a randomized order. For each choice task, respondents were asked to make two decisions:

- "Which of these is the most preferred product to reduce the risk of preterm birth?" (assessing overall treatment preferences)
- "Which of these products are you more likely to take exactly as directed by your doctor (i.e. not skip a dose, not delay a dose, etc.)?" (assessing medication adherence propensity).

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righte it onoise task based on the discrete choice experiment attribute grid								
Attribute	Product A	Product B						
Medicine administration	Medicine is injected deep into a muscle (intramuscular)	Medicine is injected just below the upper layers of the skin						
Injection needle thickness	0.8 mm     Actual thickness is 1/4 <sup>th</sup> this size     Actual thickness is 1/4 <sup>th</sup> this size       0.3 mm							
Injection needle length	1.5 in	0.5 in						
Needle visible during medicine administration	Yes	No, it is covered by a plastic case						
Medicine administration location	Hip (upper area of buttocks)	Back of either upper arm						
Time to give medicine	60 seconds	20 seconds						
1. Which of these is the <b>most preferred prod</b> - uct to reduce the risk of preterm birth?	0	0						
<ol> <li>Which of these products are you more likely to <u>take exactly as directed</u> by your doctor i.e. not skip a dose, not delay a dose, etc?</li> </ol>	0	0						

Figure 1. Choice task based on the discrete choice experiment attribute grid

These tasks were designed to elicit trade-offs to determine participant preferences. Respondents were asked to assume identical efficacy, safety, and dose for each treatment.

#### Sample design and data collection

Women between the ages of 18 to 44 years (adult women of child bearing age) were recruited from an online research panel in the United States. Participants were required to qualify into one of the following groups:

- women who have had a spontaneous singleton PTB pregnancy in the past 3 years and were not pharmacologically treated for risk reduction
- women at risk of a recurrent singleton PTB (self-reported) in the past 3 years and were treated with 17-OHPC for risk reduction

• women who were pregnant at the time of survey administration, were at risk of a singleton PTB, and were being treated with 17-OHPC for risk reduction.

These groups were representative of the currently eligible treatment population.<sup>4</sup> Participants affiliated with pharmaceutical and medical equipment manufacturers, contract research organizations, or market research and advertising firms were excluded to avoid any potential conflicts of interest.

To incorporate patient input into the DCE design and identify potential sources of response error, three web-based cognitive interviews were conducted among one participant from each group.<sup>18</sup> Based on these interviews, minor formatting and wording updates were implemented, and a 45-minute survey was administered to participants who met the inclusion criteria. As traditional sample size estimation methods are not appropriate for DCEs, the method proposed by Yang et al was used,<sup>19</sup> and a sample size of 150 was derived.

#### Analysis

All data were analyzed using SAS 9.4 software. Sample characteristics were assessed by calculating percentages or means (depending on the level of measurement). Two hierarchical Bayesian random-effects-only models were used to evaluate data from the DCE: one for overall treatment preferences and one for assessing self-reported drivers of medication adherence propensity. This analysis generates respondent-specific estimates called relative preference weights.<sup>14,20</sup> These values quantify the amount of implicit and explicit preference that each survey respondent associates with each attribute level tested in the DCE.<sup>21</sup> Each relative preference weight is only meaningful when compared with weights for every other attribute level.<sup>14</sup> (*Figure 2*)

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Figure 2. Overall treatment preferences and drivers of medication adherence propensity

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overall treatment preference or medication adherence propensity.

Table 1. Sample				· · · · ·	
		Had a singleton preterm birth (< 37 weeks) in the past 3 years and not pharmacologically treated*	At risk of a re- current singleton preterm birth in the past 3 years and treated (n=60)	Currently preg- nant, at risk of a recurrent singleton preterm birth, and being treated (n=53)	Total (n=183)
	[	(n=70)	(	(	
Age	18 - 34 years 35 - 44 years	35 (50.0%) 35 (50.0%)	41 (68.3%) 19 (31.7%)	39 (73.6%) 14 (26.4%)	115 (62.8%) 68 (37.2%)
Race/ethnicity	Non-Hispanic White Hispanic or Latino Non-Hispanic Black or African American Asian or Pacific Islander Others	57 (81.4%) 11 (15.7%) 1 (1.4%) 0 (0.0%) 1 (1.4%)	42 (70.0%) 12 (20%) 2 (3.3%) 3 (5.0%) 1 (1.7%)	44 (83.0%) 6 (11.3%) 2 (3.8%) 0 (0.0%) 1 (1.9%)	143 (78.1%) 29 (15.8%) 5 (2.7%) 3 (1.6%) 3 (1.6%)
Highest level of education	Less than a college degree Four-year college degree More than a college degree	16 (22.9%) 42 (60.0%) 12 (17.1%)	22 (36.7%) 26 (43.3%) 12 (20.0%)	14 (26.4%) 28 (52.8%) 11 (20.8%)	52 (28.4%) 96 (52.5%) 35 (19.1%)
Employment status	Employed for wages Other (self-employed, retired, out of work, etc.)	48 (68.6%) 22 (31.4%)	45 (75.0%) 15 (25.0%)	43 (81.1%) 10 (18.9%)	136 (74.3%) 47 (25.7%)
Annual household income	Less than \$60,000 \$60,000 to less than \$120,000 \$120,000 or more	17 (24.3%) 34 (48.6%) 19 (27.1%)	15 (25.0%) 35 (58.3%) 10 (16.7%)	11 (20.8%) 35 (66.0%) 7 (13.2%)	43 (23.5%) 104 (56.8%) 36 (19.7%)
Insurance status	Private insurance only (via employer or self-purchased) Public insurance only (Med- icaid, VA, DOD, Medicare, etc.) Both, private and public insurance Uninsured	30 (42.9%) 21 (30.0%) 15 (21.4%) 4 (5.7%)	33 (55.0%) 14 (23.3%) 8 (13.3%) 5 (8.3%)	26 (49.1%) 22 (41.5%) 5 (9.4%) 0 (0.0%)	89 (48.6%) 57 (31.1%) 28 (15.3%) 9 (4.9%)
Product used in most recent preg- nancy	Makena <sup>®</sup> Compounded hydroxyprogesterone caproate		40 (66.7%) 20 (33.3%)	27 (50.9%) 26 (49.1%)	67 (59.3%) 46 (40.7%)
Number of times giv Number of children of Number of preterm h Number of singleton Week of pregnancy i birth occurred	en birth in the past 5 years** given birth to in the past 5 years** pirths in the past 5 years** term births in the past 5 years** n which the most recent singleton preterm	2 2 1 1 27.8	2 2 1 31.4	1 2 1 1 27.4	2 2 1 1 29.3
*Inis group had not re **Values rounded to w	ceived pharmacological treatment for reducing t hole number	neir risk of preterm birth	l.		

# Table 1. Sample characteristics

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## **Results** Sample characteristics

A total of 1,203 women belonging to at least one of the respondent groups opted to respond to the online survey. Of these, 263 (21.9%) met the inclusion criteria, and 204 (77.6%) completed the survey. Twenty-one respondents were omitted from the sample for selecting a dummy response on a question about disease symptoms. A total of 183 respondents were included for analysis (*Table 1*).

#### **Overall treatment preferences**

With a relative preference weight of 1.29 (95% HPDI [highest posterior density interval] = 0.78-1.79), "time taken to give the medicine" was the most preferred administration-related driver of overall treatment choice; a treatment that takes 20 seconds to administer was preferred over one that takes 60 seconds. In addition, a shorter injection needle (0.5 inches vs. 1.5 inches) was preferred (relative preference weight = 1.08 [0.69-1.51]), and was the next most favored attribute. Lack of needle visibility while receiving the medicine was the third most preferred attribute (relative preference weight = 0.96 [0.40-1.54]). A subcutaneous route of administration also was a statistically significant driver of treatment choice (relative preference weight = 0.38 [0.02-0.81]), relative to an intramuscular route (*Table 2*). No statistically significant differences were observed in mean relative preference weights between respondent groups ( $\alpha = 0.05$ ).

	Had a singleton preterm birth (< 37 weeks) in the past 3 years' and not pharmacologically treated		At risk of a recurrent singleton preterm birth in the past 3 years and treated		Currently pregnant, at risk of a recurrent singleton preterm birth, and being treated	
	Mean relative preference weight	95% Cl	Mean relative preference weight	95% Cl	Mean relative preference weight	95% CI
Medicine administration Subcutaneous vs. IM	0.47	0.35 - 0.59	0.35	0.21 - 0.48	0.31	0.17 - 0.44
Injection needle thickness 0.3 mm vs. 0.8 mm	-0.13	-0.27 - 0.01	-0.05	-0.24 - 0.14	-0.06	-0.25 - 0.12
Injection needle length 0.5 in vs. 1.5 in	1.16	0.94 - 1.37	1.02	0.79 - 1.26	1.06	0.8 - 1.32
Needle visible during medicine administration No vs. Yes	0.90	0.68 - 1.12	1.12	0.85 - 1.38	0.83	0.54 - 1.12
Medicine administration location Back of either upper arm vs. hip	0.19	-0.16 - 0.54	-0.19	-0.52 - 0.15	-0.14	-0.6 - 0.33
Time to give medicine 20 secs vs. 60 secs	1.34	1.07 - 1.61	1.30	1.04 - 1.57	1.21	0.92 - 1.49
Note: No statistically significant differences observed between respondent groups ( $\alpha = 0.05$ ). Attributes that have 95% confidence intervals (CIs) including 0 (zero) are not statistically significant drivers of overall treatment choice within that respondent group.						

 Table 2. Comparing mean relative preference weights for overall treatment preferences across respondent groups

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#### Medication adherence propensity

Lack of needle visibility while receiving the medicine was the most important self-reported driver of medication adherence propensity (relative preference weight = 1.00 [0.51-1.54]). An injection time of 20 seconds was preferred over 60 seconds (relative preference weight = 0.65 [0.23-1.15]); this was the second most important driver. Having a thinner injection needle (0.3 mm vs. 0.8 mm) was the third most important driver (relative preference weight = 0.60 [0.25-0.97]). Injection needle length was the fourth most important driver, with a relative preference weight of 0.56 (0.25-0.97), and a needle length of 0.5-inch was preferred over 1.5-inches. (**Table-3**) No statistically significant differences were observed in mean relative preference weights between respondent groups ( $\alpha = 0.05$ ).

#### **Clinical nursing implications** Administration-related drivers of treatment preference

The results of this study suggest that a faster administration time, shorter injection needle, and lack of needle visibility during administration are the most preferred administration-related attributes of treatments used by women at risk of recurrent singleton PTB. The administration-related attributes most preferred by respondents were associated with subcutaneous autoinjectors. These results demonstrated congruence with the evidence presented in studies conducted in other disease areas.<sup>13,22,23,24</sup>

# Patient perceived administration-related drivers of medication adherence propensity

Literature suggests that a fear of, or aversion to, needles and needle length are key reasons for medication nonadherence to injectable treatments.<sup>11,12</sup> The evidence presented in this study is consistent with these conclusions. Lack of needle visibility was the most important driver of perceived medication adherence propensity. Other needle-specific attributes, a faster administration time, a thinner injection needle, and a shorter injection needle, also were observed to be important drivers. Thus, attributes associated with subcutaneous autoin-jectors have the potential to result in a positive impact on medication adherence.

Table 3. Comparing mean relative preference weights for medication adherence propensity across respondent groups							
	Had a singleton preterm birth (< 37 weeks) in the past 3 years and not pharmacologically treated		At risk of a recurrent singleton preterm birth in the past 3 years and treated		Currently pregnant, at risk of a recurrent singleton preterm birth, and being treated		
	Mean relative preference weight	95% Cl	Mean relative preference weight	95% Cl	Mean relative preference weight	95% Cl	
Medicine administration Subcutaneous vs. IM	0.24	0.1 - 0.39	0.16	0.02 - 0.3	0.09	-0.04 - 0.22	
Injection needle thickness 0.3 mm vs. 0.8 mm	0.59	0.43 - 0.75	0.61	0.43 - 0.8	0.60	0.41 - 0.78	
Injection needle length 0.5 in vs. 1.5 in	0.58	0.27 - 0.88	0.62	0.31 - 0.93	0.48	0.18 - 0.77	
Needle visible during medicine administration No vs. Yes	0.95	0.72 - 1.18	1.09	0.84 - 1.34	0.97	0.69 - 1.26	
Medicine administration location Back of either upper arm vs. hip	0.26	-0.07 - 0.58	0.18	-0.18 - 0.54	-0.32	-0.74 - 0.1	
Time to give medicine 20 secs vs. 60 secs	0.69	0.32 - 1.05	0.60	0.27 - 0.94	0.67	0.3 - 1.03	
Note: No statistically significant differences observed between respondent groups ( $\alpha = 0.05$ ). Attributes that have 95% confidence intervals (CIs) including 0 (zero)							

Note: No statistically significant differences observed between respondent groups ( $\alpha = 0.05$ ). Attributes that have 95% confidence intervals (CIs) including 0 (zero) are not statistically significant drivers of overall treatment choice within that respondent group.

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Women at risk of a recurrent singleton preterm birth were more likely to prefer treatments that are faster to administer and have a shorter, nonvisible needle.

#### Limitations

A convenience sample of patients was used because of feasibility constraints, which may have resulted in confounding due to unobserved factors. Also, while decisions made in a DCE are comparable to real-world decision making, they do not capture the influence of other factors, such a support network, patient-healthcare provider relationships, prior treatment history, and comorbidities; none of these factors were accounted for in this study. In addition, out of concern for potential respondent burden, the order of the attributes within each hypothetical treatment in the DCE was not changed. While this may have led to some order effects, the results do not support this hypothesis.

## **Conclusion and significance**

PTB is one of the most common causes of perinatal morbidity and mortality in developed countries.<sup>25</sup> 17-OHPC has been FDA approved as a treatment for women with a singleton pregnancy who have a history of singleton spontaneous PTB to reduce the risk for recurrent PTB. Until recently, treatment with 17-OHPC required intramuscular injections at weekly intervals. Findings from several studies suggest that fear of injection needles is a leading factor in nonadherence to treatments that involve scheduled injections. Respondents to this study survey reported a preference for an injection option that was faster, used a shorter needle that could not be seen during injection, and that was administered via the subcutaneous route. They indicated they would be more likely to adhere to treatment when these injection attributes were present.

As the healthcare provider that who women often see regularly for prenatal care, advanced practice registered nurses (APRNs) have a pivotal role in the education, management, and outcome improvement of patients at risk for recurrent PTB.<sup>26,27</sup> Because of the temporal criticality of PTB, APRNs can make an immediate and tangible difference in maternal-fetal outcomes. Being cognizant of patients' preferences and incorporating them into PTB management strategies has the potential to promote better adherence to therapy and lead to better prenatal outcomes.

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Women at risk of a recurrent singleton preterm birth were more likely to state that they would be adherent to treatments where the needle is not visible during administration, that are faster to administer, and have a shorter, thinner needle.

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Research findings suggest that a subcutaneous autoinjector may be preferred by women at risk of a recurrent singleton preterm birth over intramuscular injections, and this may have a positive impact on medication adherence.

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